

We claim:

1. A method for testing compounds for an effect on an Alzheimer's disease marker comprising

a) administering the compound to be tested to a non-human transgenic mammal, or mammalian cells derived from the transgenic mammal, wherein the transgenic mammal has a nucleic acid construct stably incorporated into the genome, wherein the construct comprises a promoter for expression of the construct in a mammalian cell and a region encoding an A β -containing protein, wherein the promoter is operatively linked to the region,

wherein the region comprises DNA encoding the A β -containing protein, wherein the A β -containing protein consists of all or a contiguous portion of a protein selected from the group consisting of

APP770, APP770 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP751, APP751 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP695, and APP695 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717,

wherein the A β -containing protein includes amino acids 672 to 714 of human APP,

wherein the promoter mediates expression of the construct such that A β_{tot} is expressed at a level of at least 30 nanograms per gram of brain tissue of the mammal when it is two to four months old, A β_{1-42} is expressed at a level of at least 8.5 nanograms per gram of brain tissue of the mammal when it is two to four months old, APP and APP α combined are expressed at a level of at least 150 picomoles per gram of brain tissue of the mammal when it is two to four months old, APP β is expressed at a level of at least 40 picomoles per gram of brain tissue of the mammal when it is two to four

months old, and/or mRNA encoding the A β -containing protein is expressed to a level at least twice that of mRNA encoding the endogenous APP of the transgenic mammal in brain tissue of the mammal when it is two to four months old; and

detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mammal, or by mammalian cells derived from the transgenic mammal, and the marker in a transgenic mammal, or by mammalian cells derived therefrom, to which the compound has not been administered, is observed,

wherein an observed difference in the marker indicates that the compound has an effect on the marker. *a*

2. The method of claim 1 wherein the A β -containing protein is selected from the group consisting of APP770; APP770 bearing a mutation in the codon encoding one or more amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, 717; APP751; APP751 bearing a mutation in the codon encoding one or more amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, 717; APP695; APP695 bearing a mutation in the codon encoding one or more amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, 717; a protein consisting of amino acids 646 to 770 of APP; a protein consisting of amino acids 670 to 770 of APP; a protein consisting of amino acids 672 to 770 of APP; and a protein consisting of amino acids 672 to 714 of APP.

Sub E1 > 27 3. The method of claim 2 wherein the DNA encoding the A β -containing protein is cDNA or a cDNA/genomic DNA hybrid, wherein the cDNA/genomic DNA hybrid includes at least one APP intron sequence wherein the intron sequence is sufficient for splicing.

28 4. The method of claim 1 wherein the promoter is the human platelet derived growth factor β chain gene promoter.

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5. The method of claim 1 wherein the region further comprises DNA encoding a second protein, wherein the DNA encoding the A β -containing protein and the DNA encoding the second protein are operative linked such that the region encodes an A β -containing fusion protein comprising a fusion of the A β -containing protein and the second protein.

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6. The method of claim 1 wherein the second protein is a signal peptide.

7. The method of claim 1 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the amount of the protein present in the transgenic mammal, or in mammalian cells derived therefrom, to which the compound has been administered.

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8. The method of claim 1 wherein the protein is selected from the group consisting of Cat D,B, Neuronal Thread Protein, nicotine receptors, 5-HT₂ receptor, NMDA receptor, α 2-adrenergic receptor, synaptophysin, p65, glutamine synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, heme oxygenase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α 1-antitrypsin, C-reactive protein, α 2-macroglobulin, IL-1 α , IL-1 β , TNF α , IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), advanced glycosylation end products, receptor for advanced glycosylation end products, COX-2, CD18, C3, fibroblast growth factor, CD44, ICAM-1, lactotransferrin, C1q, C3d, C4d, C5b-9, gamma RI, Fc gamma RII, CD8, CD59, vitronectin, vitronectin receptor, beta-3 integrin, Apo J, clusterin, type 2 plasminogen activator inhibitor, midkine, macrophage colony stimulating factor receptor, MRP14, 27E10, interferon-alpha, S100 β , cPLA₂, c-jun, c-fos, HSP27, HSP70, MAP5, membrane lipid peroxidase, protein carbonyl formation, junB, junD, fosB, fra1, cyclin D1, p53, NGFI-A, NGFI-



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10. The method of claim 9 w

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mammal, or in mammalian cells derived therefrom, to which the compound has been administered.

~~14.~~ The method of claim ~~13~~ wherein the encoded protein is selected from the group consisting of growth inhibitory factor, Cat D,B, Neuronal Thread Protein, nicotine receptors, 5-HT₂ receptor, NMDA receptor, α 2-adrenergic receptor, synaptophysin, p65, glutamine synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, heme oxygenase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α 1-antitrypsin, C-reactive protein, α 2-macroglobulin, IL-1, TNF α , IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), advanced glycosylation end products, receptor for advanced glycosylation end products, COX-2, CD18, C3, fibroblast growth factor, CD44, ICAM-1, lactotransferrin, C1q, C3d, C4d, C5b-9, gamma RI, Fc gamma RII, CD8, CD59, vitronectin, vitronectin receptor, beta-3 integrin, Apo J, clusterin, type 2 plasminogen activator inhibitor, midkine, macrophage colony stimulating factor receptor, MRP14, 27E10, interferon-alpha, S100 β , cPLA₂, c-jun, c-fos, HSP27, HSP70, MAP5, membrane lipid peroxidase, protein carbonyl formation, junB, junD, fosB, fra1, cyclin D1, p53, NGFI-A, NGFI-B, I κ B, NF κ B, IL-8, MCP-1, MIP-1 α , matrix metalloproteinases, 4-hydroxynonenal-protein conjugates, amyloid P component, laminin, and collagen type IV.

15. The method of claim 1 wherein the Alzheimer's disease marker is a behavior and the observed difference is a change in the behavior observed in the transgenic mammal to which the compound has been administered.

~~16.~~ The method of claim ~~15~~ wherein the behavior is selected from the group consisting of behavior using working memory, behavior using

reference memory, locomotor activity, emotional reactivity to a novel environment or to novel objects, and object recognition.

17. The method of claim 1 wherein the Alzheimer's disease marker is a histopathology and the observed difference is a decrease in the extent or severity of the histopathology present in the transgenic mammal to which the compound has been administered.

18. The method of claim 17 wherein the histopathology marker is selected from the group consisting of compacted plaques, neuritic dystrophy, gliosis, A β deposits, decreased synaptic density, and neuropil abnormalities.

19. The method of claim 1 wherein the Alzheimer's disease marker is cognition and the observed difference is a change in the cognition of the transgenic mammal to which the compound has been administered.

20. The method of claim 1 wherein the marker is detected or measured using RT-PCR, RNase protection, Northern analysis, R-dot analysis, ELISA, antibody staining, laser scanning confocal imaging, and immunoelectron microscopy.

21. The method of claim 1 wherein the mammals are rodents.

22. The method of claim 1 wherein the codon encoding amino acid 717 is mutated to encode an amino acid selected from the group consisting of Ile, Phe, Gly, Tyr, Leu, Ala, Pro, Trp, Met, Ser, Thr, Asn, and Gln.

23. The method of claim 22 wherein the codon encoding amino acid 717 is mutated to encode Phe.

24. The method of claim 1 wherein the codon encoding amino acid 670 is mutated to encode an amino acid selected from the group consisting of Asn and Glu, or the codon encoding amino acid 670 is deleted, and/or wherein the codon encoding amino acid 671 is mutated to encode an amino acid selected from the group consisting of Ile, Leu, Tyr, Lys, Glu, Val, and Ala, or the codon encoding amino acid 671 is deleted.

~~23~~ 23. The method of claim ~~22~~ wherein the codon encoding amino acid 670 is mutated to encode Asn, and/or the codon encoding amino acid 671 is mutated to encode Leu or Tyr.

26. The method of claim 1 wherein the promoter mediates expression of the construct such that $A\beta_{tot}$ is expressed at a level of at least 30 nanograms per gram of hippocampal or cortical brain tissue of the mammal when it is two to four months old, $A\beta_{1-42}$ is expressed at a level of at least 8.5 nanograms per gram of hippocampal or cortical brain tissue of the mammal when it is two to four months old, APP and APP α combined are expressed at a level of at least 150 picomoles per gram of hippocampal or cortical brain tissue of the mammal when it is two to four months old, APP β is expressed at a level of at least 40 picomoles per gram of hippocampal or cortical brain tissue of the mammal when it is two to four months old, and/or mRNA encoding the A β -containing protein is expressed to a level at least twice that of mRNA encoding the endogenous APP of the transgenic mammal in hippocampal or cortical brain tissue of the mammal when it is two to four months old.

27. The method of claim 1 wherein amyloid plaques that can be stained with Congo Red are present in brain tissue of the mammal.